REMARKS

I. Status of the Claims

Upon entry of this amendment, claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-83 will be pending.

II. Amendments

Claim 1 has been amended to delete "C_{1-4} alkylsulfonamide" from the list of options for R_3-R_7.

Claim 36 has been amended to recite "drug addiction, alcohol addiction" instead of "drug and alcohol addiction". This amendment is made solely to further enhance the clarity of the claim.

Claim 45 has been rewritten as two separate claims by amending claim 45 to depend from claim 37 and adding claim 83, dependent from claim 39.

Claim 81 has been added, and is directed to a method of treating obesity. The amendment is supported in the specification on p. 44 line 14 of the specification as filed.

Claim 82 has been added, and is directed to a method of treating depression. The amendment is supported in the specification on p. 44 line 4 of the application as filed.

III. Response to the Rejections under 35 U.S.C. § 112 First Paragraph Enablement Requirement

1. Enablement of Solvates

Claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-80 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. Applicants respectfully traverse the rejection.

The Office Action alleges that the specification is not adequately enabled to make solvates of the compounds according to formula I. It is alleged that *Solid State Chemistry and its Applications* by A.R. West ("West") states that solvate formation is unpredictable. It is further alleged that due to the supposed unpredictability of solvate formation, and the fact that the specification allegedly does not provide guidance on how to form solvates or provide explicit examples of solvates, that it would require undue experimentation for the skilled artisan to prepare solvates according to the invention.

Applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, unless there is a reason to doubt the objective truth of the specification. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). The initial burden of establishing a basis for denying patentability to a claimed invention therefore rests upon the examiner. *Id. See also In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Thorpe*, 777 F.2d 695 (Fed. Cir. 1985); *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984).

The gist of the grounds of rejection appears to rest on the contention that West states that solvate formation of pharmaceutical solids is unpredictable and that therefore more specific guidance and/or examples are required to provide adequate enablement of the claim as it relates to solvates. It is noted that only two pages of West, namely pages 358 and 365, have been placed into the record.

Applicants respectfully point out that the discussion in West in fact does not pertain to pharmaceutical solids at all, but rather pertains to inorganic atomic solids and minerals and therefore is entirely irrelevant to the question of enablement of the presently claimed invention. On page 1 of West, defining the field of "solid state chemistry" (to which the whole book pertains), the author makes clear that the field is primarily concerned with *inorganic atomic* solids, and not molecular solids whose properties are largely determined by the molecular structure, and where the fact that they may be "solids at room temperature is incidental". Consistent with this, the entire chapter of West, from which the examiner excises isolated

statements, is concerned solely with *atomic* inorganic solids (inorganic salts and oxides, alloys, and the like) and nowhere mentions organic compounds or pharmaceutical solids. West is therefore concerned with a completely different art from the present invention, and there is no evidence that a solvate of a pharmaceutical compound would be regarded by the artisan skilled in the pharmaceutical arts as a "solid solution". The unpredictability described by West as to whether "solid solutions" will form in the context of atomic inorganic solids does not support the Office's contention that forming a solvate of a pharmaceutical compound is extraordinarily challenging.

Even if solvate formation were somewhat unpredictable, the claims would still satisfy the enablement requirement because such experimentation as might be required to prepare salts or hydrates of the compounds of the invention would be routine and well within the capacity of the skilled artisan, and would therefore not be undue, as is demonstrated by the references cited below.

An application satisfies the enablement requirement if the disclosure has sufficient information to enable the person skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test for whether experimentation would be undue is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine. *Id* at 737. The fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. on other grounds sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976).

The issue in *Wands* was whether the patentee had adequately enabled one skilled in the art to make certain high-affinity IgM antibodies. *Wands,* 858 F.2d at 735. The PTO had rejected

the claims claiming that the production antibodies was unpredictable and unreliable, thus requiring undue experimentation. *Id.* However, the Federal Circuit reversed and made the point that even though the screening required to produce the antibodies was labor-intensive with a lot of steps (e.g., immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells, cloning the hybridoma, screening the resulting antibodies, etc.), all the methods needed to practice the invention were well known, and the amount of effort was not excessive enough to be undue *despite any unpredictability* associated with making antibodies. *Id* at 740.

In *stark* contrast with the antibody-making procedures at issue in *Wands*, the preparation of hydrates and solvates of a given organic molecule is substantially easier, overwhelmingly simpler, requires significantly fewer steps, and demands much less time than for the preparation of a monoclonal antibody. Accordingly, if the court concluded that the preparation of a monoclonal antibody was enabled *as a matter of law* despite the complex and lengthy process involved, it is unreasonable for the patent office to reject hydrates and solvates as lacking enablement given that they are infinitely simpler to make. The table below provides a step-by-step comparison of some of the major steps involved in the production of a monoclonal antibody (as disclosed in *In re Wands*) and the one step involved in making a hydrate or solvate. The experimentation involved in the production of a monoclonal antibody is tremendously more complex and time-consuming than forming a solvate, yet the court concluded that it was not excessive and undue.

Step	Monoclonal Antibody	Solvate or hydrate
1	immunize animal	Expose the compound to solvent or water
2	remove the spleen from the immunized animal	
3	separate the lymphocytes from the other spleen cells	
4	mix the lymphocytes with myeloma cells	
5	treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	
7	culture single hybridoma cells (often 100 of different cells) in separate chambers	
8	assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	
Total Time	Months	About 1-2 days

Thus, to say the rejection of the claims based upon an assertion that the preparation of solvates would require "undue" experimentation is clearly inconsistent with the Federal Circuit's holding finding that the claims to forming antibodies were enabled as a matter of law in *Wands*.

Although making monoclonal antibodies involves a greater amount and complexity of experimentation than is involved in forming solvates, the preparations of monoclonal antibodies and solvates share the characteristic that the step(s) involved are well known and routine.

Applicants provide herewith evidence that solvate is easy, simple, requires few steps, and demands little time, and that the person of skill in the art routinely engages in such experimentation, and that the techniques for performing such experimentation are well known.

To make hydrates and solvates, samples of the organic compound are simply exposed to water or various different solvents. Exposure of the organic compounds to water and various solvents is conducted through simple and routine methods such as letting the samples sit open to air for set amounts of time, as well as slurrying and/or crystallizing the samples from water or solvent. In fact, it is difficult to conceive of a scientific method that is simpler to perform than placing a powder on a dish and letting it sit out on a humid day. Other typical procedures for making and identifying hydrates and solvates are described on pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, a copy of which is provided herewith.

Once solvates are formed, they can be readily analyzed by routine methods. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Karl Fischer titrimetry, X-ray diffractions (single crystal or powder), infrared spectroscopy (IR), polarized light microscopy, and hot stage microscopy or other routine techniques to detect and quantify the presence of solvate molecules in the sample. As evidence thereof, see page 18, right column, Vippagunta et al. *Adv. Drug Delivery Rev.*, **2001**, *48*, 3-26, a copy of which is provided herewith.

While there may be many solvents and conditions to try, the screen merely uses methods that are very well known in the art and considered quite simple. In fact, the process is *so* routine as to be amenable to high throughput screening, for example high throughput crystallization as described, for example, in Morisette, *et al.*, *Adv. Drug Delivery Rev.*, **2004**, *56*, 275-300, a copy of which is provided herewith.

The Office Action attempts to base its enablement rejection solely on the alleged unpredictability of solvate formation and the fact that no specific examples of solvates have been described in the specification. The fact that the West reference fails to support the Office's allegation that forming solvates is unpredictable has been noted above. More importantly, however, *Wands* establishes that unpredictability (which was the main grounds of improper

enablement rejection in *Wands*), even if it were established, is not dispositive. Similarly, there is no requirement for a "working" example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970); *Ex parte Nardi*, 229 U.S.P.Q. 79 (Pat. Off. Bd. App. 1986). Given that one skilled in the art could make and identify various hydrates and solvates of a particular organic molecule using the routine screening methods discussed above, no working example is necessary to enable the invention. *Wands*, in fact, mandated that numerous factors be considered in evaluating enablement rather than the narrow approach taken by the Office here.

It is respectfully submitted that any unpredictability or the absence of examples of solvates specifically described as solvates or hydrates should be found to be clearly outweighed by the fact that preparing and screening for hydrates and solvates is routine and employs well-known methods. Applicants note that even a cursory search of the U.S.P.T.O. database of issued patents suggests a substantial number of pharmaceutical patents with claims referencing solvates and hydrates , yet having no enablement rejections to the same: see, e.g. Patents. Nos. 7232823, 7230024, 7230002, 7229991, 7227027, 7211591, 7173037, 7157466, and 7105523. Applicants see no difference between these patents and the present application with respect to enablement of hydrates and solvates.

Since the preparation of solvates is the type of experimentation that is routinely engaged in the art, and merely involves the use of well known methods without excessive effort, applicants respectfully request that the rejection of claims 1-3, 9, 11-12, 17, 19-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-80 under the enablement requirement of 35 U.S.C. § 112 first paragraph based upon the recitation of solvates be withdrawn.

2. Enablement of Methods of Modulating a $5HT_{2C}$ receptor

Claims 33-34 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. Applicants respectfully traverse the rejection.

As explained above, applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, and the burden of establishing a basis reason to doubt the objective truth of the specification rests upon the examiner. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)). "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

The applicants observe that the Office Action does not appear to give any reasons why claims 33-34 were rejected. The reasons given for the rejection of 33 and 34 (along with other claims) appear to state that treatment of various $5HT_{2C}$-mediated *disorders* is not reasonably enabled by the specification. Although this is disputed by the applicants, for reasons given in greater detail below, applicants fail to see how this, even if true, would support the rejections of claims 33 and 34 which are directed to modulating $5HT_{2C}$ *receptor* response. The skilled artisan could readily modulate $5HT_{2C}$ receptor response using the compounds identified in the specification because to do so merely requires contacting the receptor with the compound. On p.1 line 5 of the specification it is stated the compounds of the invention are modulators of the $5HT_{2C}$ receptor. A method for modulating the $5HT_{2C}$ receptor, and data for representative compounds are provided in Example 1. Unless the Office has reasons to doubt the objective truth of the statements (which have not been given in making the rejection), it is not seen what is the basis of the rejection.

Applicants respectfully request reconsideration of the rejection of claims 33-34 under the enablement requirement of 35 U.S.C. § 112 first paragraph, and respectfully submit that upon such reconsideration the rejection should be withdrawn.

3. Enablement of Methods of Treatment

Claims 35-37, 39, 45-46, 48-49, 51-52, 54 and 80 were rejected under the enablement requirement of 35 U.S.C. § 112 first paragraph. Applicants respectfully traverse the rejection.

The Office Action alleges that the specification is not adequately enabled to treat $5HT_{2C}$-receptor mediated disorders. No evidence is presented to support the rejection other than a citation to Cryan, *et al.*, *Hum. Psychopharmacol. Clin. Exp.*, **2000**, *15*, 113-135 ("Cryan 1"), which the Office Action claims shows "the speculative nature of the role of 5-HT receptors with the treatment of depression".

As explained above, applicants enjoy a presumption that the specification, which discloses how to make and use the claimed invention, complies with the first paragraph of 35 U.S.C. § 112, and the burden of establishing a reason to doubt the objective truth of the specification rests upon the examiner. MPEP 2164.04 (citing *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)).

Applicants respectfully point out that the specification, particularly the discussion in the Background of the Invention (and the references cited therein) presumptively establishes the utility of the compounds of the invention, as $5HT_{2C}$ agonists, in treating the various conditions identified in the rejected claims. For example, the specification states: on p.3 line 33 that a "$5HT_{2C}$ agonist can be an effective and safe anti-obesity agent"; on p. 4 line 3-7 that $5HT_{2C}$ agonists are useful as anti-panic agents, are useful for treating sexual dysfunction, psychiatric symptoms, and eating disorders; on p.6 line 14 that $5HT_{2C}$ agonists are useful for treating Alzheimer's disease. It is also stated that the compounds are useful for the various diseases in the specification on p. 43-47. These statements provide the requisite presumptive enablement. Should the Office have reason to doubt the objective truth of these statements, then the Office is respectfully reminded that the Office has a burden of providing evidence or reasoning substantiating the doubts. As the MPEP explains that in order to sustain a rejection under enablement rejection, the "factors, reasons, and evidence" leading to the rejection should be

provided, "findings of fact" should be "supported by the evidence" and that "specific technical reasons are always required." See MPEP 2164.04. Other than the citation to *Cryan 1* (which, as explained below, does not support the Office's position) no such evidence or technical reasons have been provided. The Office has therefore not met its burden of providing a reasonable explanation as to why the scope of protection claimed in the rejected method of treatment claims is not adequately enabled by the disclosure.

The alleged lack of predictability relied upon in making the rejection is refuted by the reference cited as evidence in support of it. According to the Office Action, Cryan 1 demonstrates that the role of 5-HT receptors in the treatment of depression is "speculative", citing a statement in the conclusion of the Cryan 1 that it would be necessary to "unravel the complex effects of ... *the various* postsynaptic 5-HT receptors and their significance, if any, in mediating the anti-depressant response". According to the Office, the statement indicates that the role of 5-HT receptors in the treatment of depression is "speculative". Applicants respectfully disagree with the Office's interpretation, and instead read the statement that the significance of the effects of *the various* 5-HT receptors has not been elucidated as merely indicating that the particular role in mediating anti-depressant responses has not yet been established for *every* 5-HT receptor. The applicants' view is supported by the fact that the authors of the reference specifically addressed the role of the 5-HT_{2C} receptor in antidepressant responses, concluding that it appears to play "a definite role ... in mediating the antidepressant response" (see Cryan 1, p. 124). Cryan 1 therefore tends to refute rather than support the Office's position.

In another publication, Cryan, *et al.*, *J. Pharmacol. Exp. Ther.*, **2000**, *295*, 1120-26 ("Cryan 2") (a copy of which is provided herewith), the very same author demonstrated that 5-HT_{2C} receptor selective agonists were active in animal models of depression, that the effects of antidepressants were blocked by 5-HT_{2C} receptor selective agonists. The authors indicated that "the results strongly implicate a role for 5-HT_{2C} receptors in the behavioral effects of antidepressant drugs" and were "evidence that the 5-HT_{2C} receptor may indeed be a novel target

for the development of antidepressants and perhaps of drugs effective in other psychiatric disorders involving 5-HT".

Based on the foregoing, there is no evidence to support the rejection under the enablement rejection. The only evidence cited in the Office Action is Cryan 1, which is cited as evidence that the role of 5-HT_{2C} receptors in the treatment of depression is speculative. Cryan 1 in fact is evidence to the contrary. The examiner has provided no evidence to doubt the enablement of the claims as to the treatment of any other disease or condition, or 5-HT_{2C} mediated diseases generally.

In addition to the lack of evidence supporting the Office's position, the Office errs in applying the *Wands* factors. The extensive disclosure and guidance provided by in the specification appears to have been disregarded. The Office Action overstates both the level of unpredictability and the level of validation needed in order to satisfy the enablement requirement of 35 U.S.C. § 112 first paragraph. At the same time the Office underestimates the level of skill and state of knowledge in the art, as well as the amount of experimentation typically involved in drug development. All these factors show that the quantity of experimentation required to practice the claimed invention would be far from undue.

The nature of the invention claimed in the rejected claims is that the rejected claims are all directed to the treatment of $5HT_{2C}$-mediated diseases by administering compounds according to Formula I which have been shown to modulate the $5HT_{2C}$ receptor as agonists.

As conceded by the examiner, the level of skill in the art is extremely high. The persons skilled in the art will typically be Ph.D. scientists specializing in drug discovery and development and/or medical doctors specializing in treatment of the diseases that are the subject of the claims. Those persons will be capable of designing and performing highly sophisticated experiments.

With regard to the state of the art and level of predictability in the art, the Office asserts that the state of the art as speculative and unpredictable, but the Office has provided no evidence

therefore (except for the citation to Cryan 1, which, as applicant pointed out refutes rather than supports the Office's position). As the discussion in the Background section of the specification demonstrates, numerous diseases have been linked to the $5HT_{2C}$ receptor, with animal studies in the literature supporting the therapeutic utility of $5HT_{2C}$ agonists for treating the conditions. It is respectfully submitted that the skilled artisan recognizes a link between biochemical mechanisms, pharmacological activity of compounds, and therapeutic utility that appears to have been disregarded by the Office in making the rejection. Contrary to what is asserted in the Office Action, the skilled artisan would not need to test every compound within the scope of the invention to find those which are effective in treating a given condition. It is common in the art to use a "screening cascade" starting with routine in vitro screens to identify the compounds most likely to be effective in vivo, thus avoiding undue experimentation. Routine in vitro screening methods are available to determine functional activity versus the $5HT_{2C}$ receptor (see, e.g. Example 1 of the specification) as well as other factors that are important to pharmacological activity (such as in vitro metabolism studies). Animal models which are available for the various conditions may also be used to identify which compounds are most effective versus which conditions, but may be reserved for the compounds that have demonstrated most promise in the in vitro studies.

Applicants also respectfully point out that the $5HT_{2C}$ receptor is recognized in the art as a well-validated therapeutic target for the diseases whose treatment is the subject of the rejected claims. It is well known in the art that serotonin receptor expression or activity is implicated in numerous CNS disorders including anxiety, depression, obsessive compulsive disorder, affective disorders, eating disorders, drug addiction, sexual dysfunction and the like. The following five references, which represent only a sampling of the abundant literature on the subject, demonstrate the validity of $5HT_{2C}$ receptor as a target for a variety of different CNS disorders: Wood *et al.*, *Drug Dev. Res.*, **2001**, 54, 88; Bos *et al.*, *J. Med. Chem.*, **1997**, *40*, 2762; Martin, *et al.*, *J. Pharmacol. Exp. Ther.*, **1998**, *286*, 913; Cryan *et al.*, *J. Pharmacol. Exp. Ther*, **2000**, *295*, 1120; and Grottick, *et al.*, *J. Pharmacol. Exp. Ther*, **2000**, *295*, 1183, each of which are enclosed herewith.

The applicants have provided considerable guidance and working examples for carrying out the invention, contrary to the Office's assertion that little guidance has been provided. The 109 page specification provides detailed information defining the compounds of the invention as well as defining preferred embodiments of the compounds and describing methods of making the embodiments (see pages 15-43, 61-63 and 67-97). Considerable guidance is also provided for the formulation and administration of the compounds (pages 52-61). Further, extensive guidance as to the methods of treatment is provided (see pages 43-52). This disclosure, for example, identifies numerous $5HT_{2C}$ receptor-mediated diseases (addressing the Office's concern that the skilled artisan might not know what conditions may be treated) (see pages 43-45). Screening methods are also provided (pages 65-67), as well as data for representative compounds demonstrating in vivo activity in an animal model relevant to treatment of obesity.

Although further experimentation such as obtaining clinical data might be required before a given compound would be able to be sold as a drug for the treatment of any particular disease, the absence of such data from the specification or the need for experimentation to obtain such data are not inconsistent with satisfaction of the enablement requirement. The courts have recognized that the level of validation required for patentability is much lower than required, for example, to obtain F.D.A. approval to market a new drug. *See, e.g., In re Brana*, 51 F.3d, 1560, 1568 (Fed. Cir. 1995) ("Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development."). In view of the complexity of developing the field of developing new pharmaceuticals, the quantity of experimentation required to practice the invention of the rejected claims cannot be described as undue. *Wands* recognized that the need for further experimentation is not inconsistent with enablement: "the key word is undue not experimentation". *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (quoting *In re Angstadt*, 537 F.2d 498, 504, 190 (C.C.P.A. 1976) (internal quotation marks omitted). Pharmaceutical drug discovery and development, is complex, to be sure, but the law does not preclude inventions in complex fields from patent protection. It is recognized that the fact that experimentation may be required and may be complex does not necessarily make it undue, if the art typically engages in

such experimentation. MPEP 2164.01 (citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983)). Few fields of endeavor rival the complexity of developing pharmaceuticals. It is respectfully submitted that the fact of the very high cost associated with developing a new drug (estimated to be in the range from about $500 million to $2,000 million for each new chemical entity) is reflective of the fact that drug companies "typically engage in" a substantial amount of experimentation in the course of drug development. The amount of experimentation that would be required to practice the claimed invention would therefore not be "undue".

In view of the foregoing, reconsideration of the examiner's findings concerning enablement of claims 35-37, 39, 45-46, 48-49, 51-52, 54, 59 and 79-80 is respectfully requested. It is respectfully submitted that upon such reconsideration, the examiner should conclude that the rejection for lack of enablement under 35 U.S.C. § 112 should be withdrawn.

IV. Response to the Rejections under 35 U.S.C. § 103(a)

1. Rejection of Claims 1-2, 11-12, 17, 19-26, 32 and 79 over Allen, U.S. Patent No. 3,751,417

Claims 1-2, 11-12, 17, 19-26, 32 and 79 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Allen, U.S. Patent No. 3,751,417 (the "'417 patent". Applicants respectfully traverse the rejection.

The Office Action maintains that "claim 1 of the reference renders the scope of instant claim 1 obvious" and that, "for example ... 2-methyl-1-(4-methylphenyl)-piperazine [and] 1-(4-methoxyphenyl)-2-methyl-piperazine" which are said to be disclosed in the reference, rendered the claims obvious. It is maintained that the presently claimed compounds would have been obvious because "one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1."

Patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by Congress is applied in each and every case. MPEP 2141(I). The Supreme Court recently clarified that for an invention to be obvious under § 103, the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) must be considered, including an analysis of the scope and content of the prior art and the differences between the claimed subject matter and the prior art. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007). Moreover, and importantly, an explicit rationale for why one having ordinary skill in the art would have modified the prior art in the manner claimed must be set forth. *Id.* at 1741. Indeed, "rejections on obviousness grounds *cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning* to support the legal conclusion of obviousness" *Id.* (quoting *In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)) (emphasis added).

Recent case law has made it clear that "it remains necessary to identify some reason that would have led a chemist to modify a known compound *in a particular manner* to establish *prima facie* obviousness" reaffirming that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the *specific molecular modifications* necessary to achieve the claimed invention' was also required." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995)) (emphasis added). In *Takeda*, the Federal Circuit upheld a lower court finding that a claim to an ethyl-substituted compound was not rendered obvious by a prior art disclosure of a corresponding methyl-substituted compound, in part because there was reason apparent to select the prior art methyl compound as a lead compound to modify to arrive at the claimed invention, even though it was one of only fifty four compounds specifically identified in the prior art reference. *Takeda*, 492 F.3d at 1358.

Contrary to the Supreme Court's mandate in *KSR v. Teleflex*, the prior Office Action appears to be maintained upon "mere conclusory statements". Certainly the Office Action failed, as required by *Takeda*, to identify any "reason that would have led a chemist to modify a known

compound *in [the] particular manner*" or make any "showing that the 'prior art would have suggested making *the specific molecular modifications* necessary to achieve the claimed invention."

As a preliminary matter, it is not clear to the applicants why the person of skill in the art at the time that the present invention was made would have had any reason even look to or consult the '417 patent, let alone make compounds that might be used as intermediates in making compounds disclosed therein. The '417 patent relates to a completely different problem (i.e. treatment of pain) from that addressed by the present invention (i.e. modulation of $5HT_{2C}$ receptors).

Indeed, the Office Action fails to identify any specific compounds within the scope each of the rejected claims were supposedly rendered obvious by the reference, so it is impossible to discern which specific molecular modifications the Office contends were rendered obvious by the reference, let alone the reasons for them. If, for example, it was the Office's contention that it would have been obvious for the person skilled in the art to make a particular compound within the generic disclosure of claim 1 of the '417 patent and that it would therefore have been obvious to make a particular compound within the scope of the rejected claims as an intermediate in such a synthesis, then it would be necessary for the Office to identify the reason that it would have been obvious make the particular compound in order to show that the person skilled in the art would have modified the reference in the particular manner necessary to obtain the presently claimed invention. No such reasoning appears in the Office Action in support of the rejection.

Although the Office identifies two compounds that are said to be disclosed in the reference and states that those compounds rendered the rejected claims obvious, applicants note that the compounds identified are ones that are expressly excluded from the scope of the scope of the rejected claims. Applicants fail to see how the disclosure in the reference of these compounds, which are *outside* the scope of the rejected claims, would have made it obvious for the skilled artisan to make compounds *within* the scope of the claims that expressly exclude

them. There is no rule that where a claim contains language excluding a particular compound from its scope, that the scope of what remains is obvious over the excluded compound. The Office must show why it would have been obvious to modify the reference to make compounds *within* the scope of the claims, not that the reference discloses compounds that *would* be within the scope of the claims but for language excluding them.

Applicants also respectfully point out that even if the compounds of claims 1-2, 11-12, 17, 19-26 and 79 would have been obvious in view of the '417 patent (which the applicants dispute), the examiner has not provided any reasons why a pharmaceutical composition as claimed in claim 32 would have been obvious. Applicants note that such 3-alkyl-4-arylpiperazine compounds as are disclosed in the reference are intermediates that are not disclosed as having any pharmacological activity, so it not seen for what reasons a skilled artisan would have modified the '417 patent by making pharmaceutical compositions of intermediates which are allegedly suggested by the reference.

Finally, applicants respectfully point out that even if the Office properly concluded that a prima facie case of obviousness was established by the '417 patent (which the applicants dispute), the rejection fails to take into account the fact that the useful biological activity of the presently claimed compounds would have been completely unexpected from the disclosure of the '417 patent. The MPEP reminds examiners that evidence of secondary considerations such as unexpected results must always be considered in determining whether an invention is obvious. Here any prima facie case of obviousness must be considered rebutted by the unexpected and useful biological activity exhibited by the presently claimed compounds described in the specification. Even if the '417 patent had, in some abstract sense, "suggested" compounds according to the rejected claims, the Office Action does not suggest any reason that the person skilled in the art would have expected such compounds to have any useful biological activity. That the compounds do possess such unexpected biological activity should not overcome any prima facie case the Office might have established.

Based on the foregoing, since the Office has not established that the rejected claims would have been obvious over the '417 patent, reconsideration and withdrawal of the rejection of claims 1-2, 11-12, 17, 19-26, 32 and 79 under 35 U.S.C. § 103(a) over the '417 patent is respectfully requested.

2. Rejection of Claims 1, 3, 11, 12, 17, 19-25 and 79 over Kametani *et al*, *J. Org. Chem.*, 1972, 35, 1450-53.

Claims 1, 3, 11, 12, 17, 19-25 and 79 were rejected under 35 U.S.C. § 103(a) over Kametani *et al*, *J. Org. Chem.*, **1972**, *35*, 1450-53 ("Kametani"). Applicants respectfully traverse the rejection.

The Office Action maintains that, with regard to Kametani, "[g]enerically, claim 1 [*sic*] of the reference renders the scope of instant claim 1 obvious" and "2,4-dimethyl-1-phenylpiperazine" which is said to be disclosed in the reference "render[s] claim 1 obvious". It is maintained that the presently claimed compounds would have been obvious because "one skilled in the art would have been motivated to prepare compounds as taught in the reference with the expectation of obtaining compounds falling within the generic teaching of claim 1 [*sic*]."

The statement in the Office Action referring to "claim 1 of the reference" in connection with the present rejection is not understood because the reference is a scientific publication, not a patent, and therefore has no claims. It is not understood what "generic disclosure" of "claims" of the reference the Office Action is referring to. Applicants respectfully request clarification of this aspect of the rejection.

So far as the applicants can discern, the only disclosure in Kametani that is even remotely pertinent to the present invention is the disclosure of 2,4-dimethyl-1-phenylpiperazine as a minor by-product (formed in 2.5% yield) from the reaction of bromobenzene with N,N'-dimethylpiperazine. This disclosure does not anticipate the rejected claims because 2,4-dimethyl-1-phenylpiperazine is expressly excluded from the scope of claim 1 and, as pointed out

above, there is no rule that where novelty is established using a proviso, that the scope of what remains is obvious over the excluded compound. To maintain a rejection for obviousness, the Office must rather show why it would have been obvious to modify the reference to make compounds within the scope of the claims.

Applicants respectfully submit there would have been no reason for the person skilled in the art to modify Kametani to provide compounds within the present claims because Kametani fails to disclose anything about 2,4-dimethyl-1-phenylpiperazine other than the fact that it can be isolated as a minor byproduct of a chemical reaction. Neither the reaction itself nor 2,4-dimethyl-1-phenylpiperazine are disclosed by Kametani as having any utility whatsoever. Therefore it is not seen why the person skilled in the art to which the present invention pertains would have had any reason to modify Kametani to make compounds within the scope of the rejected claims. If the Office disagrees, it is respectfully submitted that the reasons should be provided.

Based on the foregoing, since the Office has not established that the rejected claims are obvious over the Kametani, reconsideration and withdrawal of the rejection of claims 1, 3, 11, 12, 17, 19-25 and 79 is respectfully requested.

V. Conclusion

Based on the foregoing, it is respectfully submitted that the grounds of rejection have been overcome and that the application is in condition for allowance. An early action toward that end is therefore respectfully requested.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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